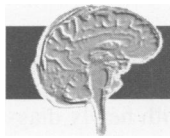

NEUROLOGY *Therapy*

Guidelines for Treating Epilepsy in the Age of Felbamate, Vigabatrin, Lamotrigine, and Gabapentin

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For the first time in 15 years, new antiepileptic medications are available for the treatment of patients with seizure disorders. These drugs have demonstrated efficacy in animal models of epilepsy and in controlled clinical trials. Felbamate was licensed in 1993 for use as adjunctive therapy or monotherapy in adults with partial or tonic-clonic seizures and as adjunctive therapy for children with the Lennox-Gastaut syndrome. Gabapentin was approved January 1994 as adjunctive therapy in patients 12 years or older with partial seizures, with or without secondary generalization. Lamotrigine is expected to be approved this year for the treatment of partial and tonic-clonic seizures in adults. Last, a new drug application has been filed for vigabatrin this year, with possible licensing next year. These four anticonvulsants present new options in the treatment of patients with refractory epilepsy and are not merely congeners of previously available treatments. They have unique clinical spectrums and are reported to be safer and better tolerated than conventional therapy. Trials to compare their use with that of conventional therapy have not been done, and their use in the initial treatment of patients with epilepsy is not completely clear.

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Despite the optimal use of the currently available anticonvulsants, many patients' seizure disorders remain refractory to treatment, or they experience intolerable side effects. In 1987 it was estimated that of the 800,000 patients in this country with partial seizure disorders, about 360,000 were considered refractory to therapy.[1] More recently a Roper poll reported patients' experience with common epilepsy medications. Of the 760 patients answering a questionnaire, 63% had recurrent seizures, 61% suffered side effects, and 44% had both side effects and recurrent seizures.[2] When evaluated for their level of satisfaction with their current epilepsy therapy, 49% were unhappy about the side effects caused by their epilepsy medications and 59% felt they had no choice but to accept this level of seizure control and side effects. Clearly there is a need for more effective, better-tolerated anticonvulsants.

The most widely used anticonvulsants, carbamazepine, phenytoin, valproic acid, and phenobarbital (referred to in this article as conventional therapy), can be highly effective for certain patients. Each medication has its own spectrum of pharmacokinetic difficulties and troublesome side effects. Behavioral and cognitive changes are common with the use of phenobarbital. The nonlinear pharmacokinetics of phenytoin can pose challenges for a clinician. A narrow separation between doses that cause central nervous system side effects and those that control seizures (that is, small protective index—discussed later) is common to both phenytoin and carbamazepine.

Conventional anticonvulsants also frequently have non-central nervous system adverse effects for patients. The long-term use of phenytoin has been associated with coarse facies, acne, hirsutism, gingival hypertrophy, and peripheral neuropathy.[3] A rash occurs in 5% to 10% of patients taking carbamazepine, as well as hyponatremia and neutropenia. In rare cases, carbamazepine use has been associated with serious hematologic toxicity, including aplastic anemia and thrombocytopenia.[4] Taking valproate has been associated with gastric irritation, hair loss, weight gain, thrombocytopenia, inhibition of platelet function, and impaired hepatic function including fatal hepatotoxicity.[5] In addition to these direct side effects, conventional anticonvulsants also demonstrate major drug interactions that can produce substantial adverse effects or difficulties in administration.

Before the licensing of felbamate last fall, it had been 15 years since a new anticonvulsant was introduced in

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ABBREVIATIONS USED IN TEXT

FDA = Food and Drug Administration
GABA = γ-aminobutyric acid
MRI = magnetic resonance imaging

the United States. Gabapentin approval followed shortly (January 1994). Lamotrigine is expected to receive its final approval this year, and vigabatrin will probably be licensed for use in 1995. These four drugs represent anticonvulsants whose spectrum of action, side-effect profiles, and pharmacokinetics are substantially different from the anticonvulsants already licensed. In this article I will review these new anticonvulsants and make recommendations regarding their role in the treatment of patients with epilepsy.

Felbamate

Felbamate (Felbatol, Wallace Laboratories) was approved by the Food and Drug Administration (FDA) in 1993 for use as adjunctive or monotherapy in adults with partial seizures and as adjunctive therapy for the treatment of the Lennox-Gastaut syndrome in children. The mechanism of action of felbamate is not known. Felbamate demonstrates an anticonvulsant effect in models of seizure spread (maximal electroshock) and seizure threshold (pentylenetetrazol), with a spectrum similar to that for valproate but with a wider protective index—the ratio between the dose that produces toxicity in 50% of animals and the dose that inhibits seizures in 50% of the animals (Table 1).[6] Felbamate demonstrates a number of drug interactions, causing increases in the blood concentrations of phenytoin, valproate, and the epoxide metabolite of carbamazepine.[7] Side effects include insomnia, weight loss, and gastrointestinal complaints and infrequently require the drug to be discontinued.[8]

Several controlled clinical trials have demonstrated the efficacy of felbamate in the treatment of refractory partial seizures, and a double-blind, add-on trial proved felbamate effective in children with the Lennox-Gastaut syndrome. In addition to notable reductions of tonic, atonic, and atypical absence seizures, an assessment of the quality of life of treated patients showed substantial improvement.[9] Trials of felbamate in juvenile myoclonic epilepsy and infantile spasms have shown promising results.[10,11] Although the package insert gives dosing information for initial therapy in adults, felbamate has not been systematically studied in patients with newly diagnosed epilepsy.

TABLE 1.—*Protective Indexes of the New Anticonvulsants (in Mice)*

Drug	Protective Index	
	Maximal Electroshock	Pentylenetetrazol
Phenytoin	6.3	NE
Carbamazepine	14.1	NE
Valproate	1.9	3.3
Ethosuximide	NE	4.4
Felbamate	38	20
Gabapentin	NA	NA
Lamotrigine	80	NE
Vigabatrin	NE	NE

NA = effective but median toxic dose not available, NE = not effective

In children the initial dose is usually 15 mg per kg of body weight daily in three divided doses with increases of 15 mg per kg weekly. The initial dose in adults is 400 mg three times a day, with weekly increases of 600 to 1,200 mg per day. Doses as high as 3,600 mg per day were used in the pivotal studies reported to the FDA, but doses of 4,800 mg per day or greater have been tried without serious side effects. When initiating felbamate therapy in patients taking carbamazepine, phenytoin, or valproate, the concomitant medication should be reduced by about 25%.

Gabapentin

Gabapentin (Neurontin, Parke-Davis Pharmaceutical Research) was approved for use by the FDA early in 1994 as adjunctive therapy in patients 12 years of age or older with partial seizures with or without secondary generalization. It is water-soluble, has low toxicity, and is not metabolized by the liver, being excreted essentially unchanged by the kidney. It is not bound to plasma proteins, and no serious drug interactions have been described.[12] In studies of chronic toxicity, acinar cell adenocarcinomas of the pancreas developed in male rats.[13] The relevance of these tumors in male rats to carcinogenic risk in humans is unclear, as human pancreatic tumors are typically ductal in origin rather than of acinar cell origin.

The mechanism of action of gabapentin is not known. Gabapentin was synthesized as a structural analogue of γ-aminobutyric acid (GABA) that could penetrate the blood-brain barrier and mimic the actions of GABA in the brain. This is not the case, however. It has no effect on the concentration of GABA in the brain, is not metabolically converted to GABA or a GABA agonist, and does not interact with GABA receptors.[14] Gabapentin also does not show affinity for any of the other common receptor sites.

Gabapentin has demonstrated efficacy as adjunctive therapy in 5 controlled studies and 18 uncontrolled studies of patients with partial seizures that are medically refractory.[15] In these studies about 26% of the patients had a 50% or greater reduction in seizure frequency (Table 2).[16-19] Adverse events were usually mild in intensity and included somnolence, dizziness, ataxia, nystagmus, diplopia, and tremor.

Gabapentin is administered three times a day and is not affected by food. Typical dosages range between 900 and 1,800 mg per day and can be achieved within three days of initiating therapy. Dosage adjustments are required in patients with compromised renal function or in patients undergoing hemodialysis.

Lamotrigine

Lamotrigine (Lamictal, Burroughs Wellcome Company) is structurally unrelated to any existing epileptic drug and is a member of the phenyltriazine class. A new drug application was submitted to the FDA in December 1991, and approval is expected this year. It is already li-

TABLE 2.—*Controlled Trials of Anticonvulsant Drugs in Partial Epilepsy*

Drug	% Decrease	% Responders
Felbamate	23*	NA
Gabapentin	29	26
Lamotrigine	36	27
Vigabatrin	50	50
Carbamazepine	83†	52‡
Valproate	NA	73§

NA = not available

*A crossover trial.[16] †From Rodin et al.[17] Patients had complex partial seizures.
‡From Kutt et al.[18] §From Dean and Penry.[19]

censed for use in the United Kingdom, Ireland, Brazil, and Greece. Lamotrigine is a weak inhibitor of the enzyme dihydrofolate reductase in vitro and was screened for anticonvulsant activity when it was thought that antiepileptic drugs might act through an antifolate mechanism. In clinical studies, lamotrigine did not affect blood folate levels,[20] and pharmacologic studies suggest that lamotrigine acts at voltage-sensitive sodium channels to stabilize neural membranes and inhibit the release of excitatory amino acid neurotransmitters.[21]

Animal models of epilepsy suggested lamotrigine would have use in the treatment of partial seizures and generalized tonic-clonic seizures.[22] In controlled studies in humans, lamotrigine showed a dose-response efficacy, with about 33% of the patients having a 50% or greater decrease in seizure frequency.[23] The most frequently reported adverse events included dizziness, diplopia, headache, and ataxia. About 10% of patients experienced a rash.[24]

Lamotrigine is metabolized predominantly by glucuronic acid conjugation, and the inactive metabolite is eliminated by renal excretion. About 55% of the drug is bound to plasma proteins.[25] Although lamotrigine has no effect on the concentrations of conventional anticonvulsants, the reverse is not the case. In patients taking enzyme-inducing anticonvulsants (phenytoin, carbamazepine, or barbiturates), the elimination half-life is substantially decreased. In contrast, valproate significantly prolongs the elimination half-life of lamotrigine.[26]

Because of these considerable interactions, a complicated dosing schedule is required. The initial recommended dose of lamotrigine in patients receiving enzyme-inducing anticonvulsants is 50 mg twice a day, with increases of 100 mg each week. The maintenance dose ranges from 300 to 500 mg per day given in two doses. For patients receiving valproate, the recommended initial dose is 50 mg daily, with increases every two weeks to a maintenance dose of 100 to 200 mg per day. There is little experience in using lamotrigine in patients with either impaired renal or hepatic function. Because lamotrigine is extensively metabolized by the liver before excretion, caution should be used in such patients.

Vigabatrin

Vigabatrin (Sabril, Marion Merrell-Dow Inc) is the first of a new class of antiepileptic drugs that work by the selective, irreversible inhibition of GABA transaminase, the enzyme responsible for the metabolism of GABA. Cerebrospinal fluid measurements taken before and after treatment with vigabatrin in patients with medically refractory, complex partial seizures reveal a dose-dependent increase in total GABA, free GABA, and homocarnosine (histidine-GABA dipeptide) levels.[27]

Vigabatrin was undergoing clinical testing in the United States, but the trials were halted in 1983 when white matter degeneration occurred in mice, rats, and dogs.[28] The white matter changes (intramyelinic edema) were not associated with segmental demyelination and were reversible with the cessation of treatment. Patients with exposure to vigabatrin who subsequently underwent neurosurgical procedures and patients who died of other causes did not show these changes. In animals the white matter changes correlated with changes in magnetic resonance imaging (MRI) scans and sensory evoked potentials.[29] Laboratory tests including MRI scans and evoked potentials in humans undergoing treatment with vigabatrin have failed to elicit any evidence of serious systemic, neurologic, or neurophysiologic toxicity.[30] For these reasons clinical trials in the United States have resumed, and a new drug application is expected to be filed with the FDA in 1994. Vigabatrin is already marketed in 35 countries, predominantly in Europe.

Vigabatrin is neither protein-bound nor metabolized by the microsomal oxidase enzyme system. Vigabatrin could be given once or twice a day because of its prolonged pharmacodynamic effect; it is better tolerated on a three-times-a-day schedule. Few drug interactions have been reported with vigabatrin use, although a slight decrease in phenytoin levels has been described.[31] Vigabatrin is primarily eliminated by glomerular filtration, and therefore dosage adjustment will probably be necessary in patients with impaired renal function. Adverse effects appear to be infrequent and mild and include drowsiness, irritability, nervousness, dizziness, headache, or confusion. Less commonly reported side effects include weight gain and psychosis.[32] Despite the delay between the cessation of vigabatrin and the time required to resynthesize GABA transaminase, it appears that vigabatrin should be withdrawn slowly. A dramatic increase in seizures including status epilepticus has been described after vigabatrin was abruptly discontinued.[33]

Vigabatrin has been evaluated extensively in Europe and in the United States. Controlled multiple-dose trials of patients with refractory partial seizures found that about half of the patients had a 50% reduction in seizure frequency (Table 2). There was no increase in efficacy above 3 grams per day, but side effects were more common at the higher dose.[34] Trials of vigabatrin in children have been done only in Europe, and some efficacy has been found with partial and generalized seizures and the Lennox-Gastaut syndrome.[35] In children with infantile spasms refractory to corticotropin therapy, 75% have had a decrease in seizure frequency.[36] Increased seizure frequency with the use of vigabatrin has been reported in

patients with nonprogressive myoclonic epilepsy and absence seizures.[37]

Conventional Anticonvulsants

Previous controlled trials directly comparing phenytoin, carbamazepine, or valproate did not show one compound to be more efficacious than the others.[38,39] Therefore, when choosing an anticonvulsant, measures other than efficacy become important, including ease of administration, side-effects profile, and cost. The lessons learned from using conventional anticonvulsants also apply to the new anticonvulsants.

Direct comparisons among the new anticonvulsants or with conventional anticonvulsants have not been done, and there is no evidence to suggest one medication is superior to another. A double-blind trial of carbamazepine versus placebo was done in patients admitted to a hospital with intractable psychomotor epilepsy, and the secondarily generalized seizures were found to be decreased by 55% and the psychomotor seizures by 83%.[17] In a similar study, 52% of patients had a 50% decrease in seizure frequency.[18] Obviously, patients are considered refractory only when the available medications of the time have failed them. Patients in the carbamazepine trials had not been selected on the basis of failed trials of carbamazepine or valproate, and their seizures would possibly be less refractory than those in patients in recent trials. Similarly, of 30 patients with refractory complex partial seizures, 22 (73%) who were changed to valproate monotherapy had greater than a 50% reduction in seizure frequency.[19] Direct comparisons are difficult, but these studies do not clearly demonstrate a superiority for one anticonvulsant, conventional or new.

The new anticonvulsants have been priced to be comparable to valproate at the high end of cost. Phenytoin, because of its low cost (Table 3) and long half-life, allowing once-a-day dosing, should be the drug of choice for patients with partial seizures with and without secondary generalization. Because of gingival hypertrophy, hirsutism, and coarsening of facial features, however, carbamazepine replaces phenytoin in children. Despite the comparable efficacy in partial epilepsy, there is preliminary evidence that valproate is the drug of choice in patients with primary generalized epilepsies with spike-and-wave discharges in their electroencephalograms (Table 4).[40]

Of the new anticonvulsants, vigabatrin has had the most use to date and is being used as add-on therapy in Europe in patients whose initial treatment with carbamazepine or valproate failed to control their seizures. Considerably less information is available regarding the use of felbamate, gabapentin, and lamotrigine, but with increased patient exposures the ultimate role of these medications will be determined. All the new anticonvulsants show roughly equivalent efficacy against partial seizures with or without secondary generalization in patients whose seizures are uncontrolled by conventional medications. Lamotrigine may make patients with myoclonic seizures worse. In the Lennox-Gastaut syndrome, lamotrigine does not affect atonic or tonic seizures.[41] Felbamate, on the other hand, is effective in the Lennox-Gastaut syndrome.

TABLE 3.—*Name-Brand Anticonvulsants*

Drug	Generic	Price, $*	Typical Dose, mg/day	Cost/Day, $
Dilantin . . .	Phenytoin	18.07	300-400	0.54-0.72
Tegretol . . .	Carbamazepine	34.66	600-1,200	1.04-2.08
Depakote . .	Divalproex sodium (valproate)	56.29	750-3,000	1.69-6.23
Felbatol . . .	Felbamate	66.00	2,400-3,600	2.64-3.96
Neurontin .	Gabapentin	90.04	900-1,800	2.70-5.40

*Average wholesale price January 1994 per 100 tablets.

Little evidence exists that helps physicians decide in which order to try these new agents. Based on experiments in animals and limited clinical experience, some suggestions can be made. Drugs with large protective indexes have a wider available dose range before toxicity is reached. Table 1 compares the protective indexes in two animal models for the conventional and new anticonvulsants. Using this approach, felbamate appears to have a therapeutic spectrum similar to that of valproate, with efficacy in treating partial, tonic-clonic, and absence seizures, but with a greater protective index. This has been confirmed in clinical trials. Felbamate has shown efficacy in both partial and generalized epilepsies with minimal toxicity. As predicted by the models, lamotrigine has a clinical spectrum similar to that of phenytoin, but with a wider "therapeutic window." Vigabatrin, on the other hand, demonstrates some efficacy in animal models of human epilepsy, but preliminary evidence suggests that some patients may have their absence seizures made worse by vigabatrin use.

To date, only one study has compared the use of a new anticonvulsant with that of conventional therapy. The use of vigabatrin was compared with that of carbamazepine in medically refractory patients with partial seizures. It showed a similar efficacy, but was slightly better tolerated.[42] Until controlled trials are done comparing the use of these drugs with that of conventional therapy in newly diagnosed patients, the use of the new anticonvulsants must be limited to medically refractory patients. In patients with juvenile myoclonic epilepsy or absence epilepsy refractory to valproate monotherapy, felbamate is probably the next medication to be tried. When vigabatrin becomes available, with its unique mechanism of action, it may have a role as rational polytherapy in patients with medically refractory epilepsy. Vigabatrin and gabapentin should be the easiest to prescribe because they lack drug interactions and have little protein binding. Gabapentin has the ability to be rapidly initiated and can be quickly tried in patients before their seizures are considered refractory.

These new anticonvulsants are reported to be safer and better tolerated than conventional therapy. This may indeed be the case; however, the limited human exposure may explain the lack of substantial allergic reactions. For

TABLE 4.—*Conventional and New Antiepileptic Drugs*

Generic Name	*Trade Name*	*Indications (Seizure Types)*	*Typical Dose, mg/day*	*Half-Life, hr*	*% Bound*	*Most Common Side Effects*
Phenytoin	Dilantin	Partial with or without seizure generalization; generalized tonic-clonic*	300-400	24-30	90	Gum hyperplasia, hirsutism
Carbamazepine	Tegretol	Partial with or without seizure generalization; generalized tonic-clonic*	600-1,200	8-12	75	Neutropenia, rash, hyponatremia
Phenobarbital	Luminal	Partial with or without seizure generalization; generalized tonic-clonic*	60-120	72	50	Behavioral changes
Divalproex sodium (valproate)	Depakote	Partial with or without seizure generalization; generalized tonic-clonic; absence; myoclonic*	750-3,000	6-12	90-95	Weight gain, hair loss, GI complaints
Felbamate	Felbatol	Partial with or without seizure generalization; generalized tonic-clonic; absence; myoclonic*	2,400-3,600	20-24	25	Insomnia, weight loss, GI complaints
Gabapentin	Neurontin	Partial with or without seizure generalization in patients >12 years old	900-1,800	5-6	0	Somnolence, dizziness
Lamotrigine	Lamictal	Pending†	300-700	24‡	55	Rash, dizziness
Vigabatrin	Sabril	Pending†	3,000-4,000	NA§	0	Drowsiness, irritability

GI = gastrointestinal, NA = not applicable

*Approved for use as monotherapy.

†Probably will be approved with indications similar to those for gabapentin.

‡Excretion half-life increases to about 72 hr with concomitant administration of valproate and decreases to about 13 hr when used with hepatic enzyme-inducing medications.

§Excretion half-life is not equal to pharmacodynamic half-life.

example, in the United States, approximately 275,000 people were taking valproate in 1993. The incidence of fatal hepatotoxicity is about 1 in 118,000 patients (all ages, as monotherapy).[43] By comparison, in the manufacturer's new drug application to the FDA, the exposure of 4,000 humans to felbamate was summarized. An absence of idiosyncratic drug reactions could be due to sampling error.

None of these drugs have demonstrated teratogenicity in animals, but there is no evidence suggesting that they are less harmful to a developing fetus than conventional anticonvulsants. Therefore, their use during pregnancy or in women of child-bearing age should be limited to women who have no other alternatives for seizure control.

Although the new anticonvulsants appear promising, physicians must not be swayed by intensive advertising campaigns or aggressive drug detail agents extolling the virtues of these new agents. The fascination clinicians have for new medications needs to be tempered by the uncertainties of unknown idiosyncratic drug reaction profiles, the limited database available on drug interactions, and the increased costs to patients.

Addendum

Since this article was submitted, the FDA in conjunction with Wallace Laboratories has recommended that patients be withdrawn from felbamate therapy. There have been ten cases of aplastic anemia, including two deaths, of a total of more than 100,000 patients taking felbamate. All of the cases of aplastic anemia appeared between two and six months after therapy was initiated. This incidence is about 50 times greater than that seen in the general population. The drug has not been recalled, but the FDA and Wallace Laboratories, as well as the Epilepsy Foundation of America, have recommended that the use of felbamate be suspended, unless the benefits of continued use clearly outweigh the possible risks. Unfortunately, sequential laboratory tests do not predict those patients who are at risk for this complication.

REFERENCES

1. Dreifuss FE: Goals of surgery for epilepsy. *In* Engel J (Ed): Surgical Treatment of the Epilepsies. New York, NY, Raven Press, 1987, pp 31-49

2. Living With Epilepsy—Report of a Roper Poll of Patients on Quality of Life. New York, NY, Roper Organization Inc, 1992

3. Wilder BJ, Rangel RJ: Phenytoin: Clinical use, chap 14, *In* Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE (Eds): Antiepileptic Drugs, 3rd Edition. New York, NY, Raven Press, 1989, pp 233-239

4. Loiseau P, Duché B: Carbamazepine: Clinical use, chap 37, *In* Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE (Eds): Antiepileptic Drugs, 3rd Edition. New York, NY, Raven Press, 1989, pp 533-554

5. Bourgeois BFD: Valproate: Clinical use, chap 44, *In* Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE (Eds): Antiepileptic Drugs, 3rd Edition. New York, NY, Raven Press, 1989, pp 633-642

6. Mattson RH: General principles: Selection of antiepileptic drug therapy, chap 6, *In* Levy R, Mattson R, Meldrum B, Penry JK, Dreifuss FE (Eds): Antiepileptic Drugs, 3rd Edition. New York, NY, Raven Press, 1989, pp 103-115

7. Graves NM, Holmes GB, Fuerst RH, Leppik IE: Effect of felbamate on phenytoin and carbamazepine serum concentrations. Epilepsia 1989; 30:225-229

8. Bourgeois MD, Leppik IE, Sackellares JC, et al: Felbamate: A double-blind controlled trial in patients undergoing presurgical evaluation of partial seizures. Neurology 1993; 43:693-696

9. Felbamate Study Group in Lennox-Gastaut Syndrome: Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 1993; 328:29-33

10. Sachdeo RC, Murphy JV, Kamin M: Felbamate in juvenile myoclonic epilepsy (Abstr). Epilepsia 1992; 33(suppl 3):118

11. Espe-Lillo J, Ritter FJ, Frost MD: Safety and efficacy of felbamate in treatment of infantile spasms (Abstr). Epilepsia 1993; 34(suppl 6):110

12. Foot M, Wallace J: Gabapentin. Epilepsy Res 1991; 3(suppl):S109-114

13. Fisher RS: Emerging antiepileptic drugs. Neurology 1993; 43:S12-20

14. Chadwick D: Gabapentin. Epilepsy Res 1991; 3(suppl):S183-186

15. US Gabapentin Study Group No. 5: Gabapentin as add-on therapy in refractory partial epilepsy: A double-blind placebo-controlled, parallel-group study. Neurology 1993; 43:2292-2298

16. Jensen PK: Felbamate in the treatment of refractory partial-onset seizures. Epilepsia 1993; 34(suppl 7):S25-S29

17. Rodin EA, Rim CS, Rennick PM: Effect of carbamazepine on patients with psychomotor epilepsy: Results of a double-blind study. Epilepsia 1974; 15:547-561

18. Kutt S, Solomon G, Wasterlain C, Peterson H, Louis S, Carruthers R: Carbamazepine in difficult to control epileptic outpatients. Acta Neurol Scand 1975; 60:27-32

19. Dean C, Penry JK: Valproate monotherapy in 30 patients with partial seizures. Epilepsia 1987; 28:605

20. Sander JW, Patsalos PN: An assessment of serum and red blood cell folate concentrations in patients with epilepsy on lamotrigine therapy. Epilepsy Res 1992; 13:89-92

21. Leach MJ, Marden CM, Miller AA: Pharmacological studies on lamotrigine, a novel potential antiepileptic drug—II. Neurochemical studies on the mechanism of action. Epilepsia 1986; 27:490-497

22. Miller AA, Wheatley P, Sawyer DA, Baxter MG, Roth B: Pharmacological studies on lamotrigine, a novel potential antiepileptic drug: I. Anticonvulsant profile in mice and rats. Epilepsia 1986; 27:483-489

23. Richens A, Yuen AW: Overview of the clinical efficacy of lamotrigine. Epilepsia 1991; 32:S13-16.

24. Matsuo F, Bergen D, Faught E, et al: Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. Neurology 1993; 43:2284-2291

25. Ramsay RE, Pellock JM, Garnett WR, et al: Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with epilepsy. Epilepsy Res 1991; 10:191-200

26. Peck AW: Clinical pharmacology of lamotrigine. Epilepsia 1991; 32(suppl 2):S9-12

27. Kälviäinen R, Halonen T, Pitkänen A, Riekkinen PJ: Amino acid levels in the cerebrospinal fluid of newly diagnosed epileptic patients: Effect of vigabatrin and carbamazepine monotherapies. J Neurochem 1993; 60:1244-1250

28. Graham D: Neuropathology of vigabatrin. Br J Clin Pharmacol 1989; 27:S43-45

29. Arezzo JC, Schroeder CE, Litwak MS, Steward DL: Effects of vigabatrin on evoked potentials in dogs. Br J Clin Pharmacol 1989; 27:S53-60

30. Liegeois-Chauvel C, Marquis P, Gisselbrecht D, Pantieri R, Beaumont D, Chauvel P: Effects of long-term vigabatrin on somatosensory-evoked potentials in epileptic patients. Epilepsia 1989; 30(suppl 3):S23-25

31. Rimmer EM, Richens A: Interaction between vigabatrin and phenytoin. Br J Clin Pharmacol 1989; 27:S27-33

32. Sivenius J, Ylinen A, Murros K, Mumford JP, Riekkinen PJ: Vigabatrin in drug-resistant partial epilepsy: A 5-year follow-up study. Neurology 1991; 41:562-565

33. Reynolds EH, Ring HA, Farr IN, Heller AJ, Elwes RD: Open, double-blind, and long-term study of vigabatrin in chronic epilepsy. Epilepsia 1991; 32:530-538

34. Grant SM, Heel RC: Vigabatrin: A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. Drugs 1991; 41:889-926

35. Herranz JL, Arteaga R, Farr IN, Valdizan E, Beaumont D, Armijo JA: Dose-response study of vigabatrin in children with refractory epilepsy. J Child Neurol 1991; Suppl 2:S45-51

36. Chiron C, Dulac O, Beaumont D, Palacios L, Pajot N, Mumford J: Therapeutic trial of vigabatrin in refractory infantile spasms. J Child Neurol 1991; Suppl 2:S52-59

37. Dulac O, Chiron C, Luna D, et al: Vigabatrin in childhood epilepsy. J Child Neurol 1991; Suppl 2:S30-37

38. Mattson RH, Cramer JA, Collins JF, et al: Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. N Engl J Med 1985; 313:145-151

39. Mattson RH, Cramer JA, Collins JF: A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. N Engl J Med 1992; 327:765-771

40. Dhuna A, Pascual-Leone A, Talwar D: Exacerbation of partial seizures and onset of nonepileptic myoclonus with carbamazepine. Epilepsia 1991; 32:275-278

41. Timmings PL, Richens A: Lamotrigine as an add-on drug in the management of Lennox-Gastaut syndrome. Eur Neurol 1992; 32:305-307

42. Kälviäinen R, Aikiä M, Partanen J, Sivenius J, Mumford J, Saksa M, Riekkinen PJ: Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: An interim report. J Child Neurol 1991; Suppl 2:S60-69

43. Dreifuss FE, Langer DH, Moline KA, Maxwell JE: Valproic acid hepatitis fatalities. Neurology 1989; 39:201-207